Potent Antiemetic Effects of the New Serotonin Antagonists

PATIENTS CONSISTENTLY rank chemotherapy-induced emesis first among the adverse effects associated with oncologic treatment. Two thirds of the more than 30 effective antineoplastic agents can precipitate moderate to severe nausea and vomiting. Chemotherapy-induced emesis not only affects patients' quality of life but also their general medical condition through electrolyte disturbances, anorexia, cachexia, Mallory-Weiss tears, and aspiration pneumonia. Consequently, patients frequently withdraw from chemotherapy.

Chemotherapy-induced emesis is a complex process with many causes. Assorted afferents stimulate the emetic center located in the lateral reticular formation of the medulla oblongata, which initiates and coordinates the complex somatic and visceral actions of emesis. These triggering afferents include a humoral pathway by the chemoreceptor trigger zone, peripheral pathways in the gastrointestinal tract, and central pathways through the vestibular, limbic, and midbrain systems. Although the neuroanatomy of the emetic process has been recognized for decades, neurohumoral details have been shown only in the past several years. This knowledge provides the means for a more selective and effective prevention of chemotherapy-induced emesis.

The chemoreceptor trigger zone is located in the floor of the fourth ventricle, where it is bathed by blood and cerebrospinal fluid, and contains receptors for dopamine, serotonin, opiates, and histamine. Early antiemetic trials largely employed phenothiazines, butyrophenones, metoclopramide hydrochloride, cannabinoids, and corticosteroids alone or in combination in an attempt to block dopaminergic, presumed higher cortical, and putative peripheral receptors. Results of these trials showed only modest efficacy. More modern regimens using high-dose metoclopramide, usually in combination with dexamethasone and lorazepam, demonstrated greater success. Unfortunately, these regimens are relatively complex, expensive, and frequently associated with unpleasant side effects, including sedation, diarrhea, and extrapyramidal reactions. Subsequent research revealed that the chemoreceptor trigger zone and the vagal afferents in the small bowel are rich in a serotonin-receptor subtype, 5-hydroxytryptamine$_3$ (5-HT$_3$). Because the enterochromaffin cells in the small bowel contain serotonin, it was conjectured that acute emesis less than 24 hours after chemotherapy may in part be due to a chemotherapy-mediated release of serotonin from these enterochromaffin cells. This serotonin may stimulate the 5-HT$_3$ receptors of the chemoreceptor trigger zone and those on afferent vagal fibers, either of which, in turn, could trigger the emetic center.

Intravenously administered ondansetron hydrochloride (Zofran [Glaxo, Inc, Research Triangle Park, NJ]) is the first of several highly selective, competitive 5-HT$_3$ receptor antagonists to receive approval from the US Food and Drug Administration (FDA) for chemotherapy-induced emesis. In Europe both ondansetron and granisetron are available. In published trials involving more than 2,500 patients, ondansetron proved to be superior to previously available antiemetics in the control of acute chemotherapy-induced emesis in both cisplatin- and non–cisplatin-containing regimens. Indeed, ondansetron provides 72% major or complete antiemetic response versus 41% for high-dose metoclopramide in patients receiving cisplatin. This benefit is amplified by ondansetron's highly favorable toxicity profile (mild headaches and rare transient aminotransferase elevations) and its lack of antidopaminergic complications, such as extrapyramidal reactions. An equally effective oral formulation is available in Europe and is pending FDA approval. Like metoclopramide, ondansetron's efficacy is enhanced by adding dexamethasone (complete short-term response greater than 90%), supporting the important but as yet poorly understood role of inflammatory mediators in chemotherapy-induced emesis.

Of note, ondansetron's antiemetic effects are associated primarily with the acute chemotherapy-induced emesis and are distinctly less pronounced with the delayed-phase (more than 24 hours) type. In fact, in delayed emesis, its efficacy is reportedly no better than, and in some series inferior to, that of metoclopramide. Nonetheless, because of its favorable toxicity profile, patients prefer it to metoclopramide even in this setting.

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REFERENCES

Andrews PLR, Rapeport WG, Sanger GJ: Neuropharmacology of emesis induced by anticancer therapy. Trends Pharmacol Sci 1988; 9:334-341

Cubeddu L, Hoffman I, Fuenmayor N, et al: Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med 1990; 322:810-816

Gralla RJ, Tyson LB, Kris MG, Clark RA: The management of chemotherapy-induced nausea and vomiting. Med Clin North Am 1987; 72:289-300

Roila F, Tonato M, Cognetti F, et al: Prevention of cisplatin-induced emesis: A double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. J Clin Oncol 1991; 9:675-678

Recent Advances in Diagnostic Tests for Syncope

SYNCOPE AFFECTS 30% to 50% of the adult population and accounts for about 300,000 emergency department visits each year. Despite an estimated cost of $750 million spent on diagnostic tests for patients admitted to hospital, the cause of syncope remains unknown in more than 40% of patients. A rational approach to the diagnosis and management of syncope is essential.

The history and physical examination remain the most critical part of the initial evaluation of a patient with syncope. Of those patients to whom a diagnosis can be assigned, the history and physical examination identify the cause as much as 85% of the time. Except for the diagnosis of arrhythmias, most other causes of syncope are strongly suggested by the initial history and findings of a physical examination. An initial electrocardiogram or rhythm strip can detect a precipitating arrhythmia in 2% to 11% of patients and cardiac monitoring does so in an additional 3% to 27%. In patients who remain undiagnosed, several different approaches can be used.

While electrophysiologic studies are increasingly used in the workup of patients with syncope, not every person needs or benefits from these invasive and expensive tests. These studies are valuable for assessing life-threatening ventricular tachyarrhythmias and less helpful in determining bradyarrhythmic causes of syncope. The studies have their greatest diagnostic yield in patients with known heart disease manifested by depressed ventricular function or an abnormal electrocardiogram or Holter monitoring.

Signal-averaged electrocardiography is a diagnostic test that helps identify those patients who would benefit from

electrophysiologic studies. This noninvasive technique detects low-amplitude, high-frequency signals at the terminal portion of the QRS complex. In patients with syncope, the presence of these signals appears to have a sensitivity and specificity of 80% to 90% for eliciting serious ventricular arrhythmias by electrophysiologic studies.

Although frequently ordered, ambulatory Holter monitoring may not define an exact cause of syncope because of the lack of well-established criteria for interpreting abnormal results. To determine a specific cause for syncope, the recorded arrhythmia must coincide with the patient's symptoms, but this occurs in only 3% to 5% of cases. Some arrhythmias are common among the general population. For example, bradycardia (less than 40 beats per minute), brief runs of supraventricular tachycardia, premature ventricular contractions, and even multiform or paired premature ventricular contractions have been recorded in substantial percentages of asymptomatic ambulatory patients. The optimal duration of monitoring has also not been determined. Patient-activated intermittent recorders, loop recorders, and transtelephonic electrocardiographic recordings are useful alternatives in patients in whom an arrhythmic cause is strongly suspected.

In patients without known heart disease, the head-up tilt test can be useful in diagnosing vasovagal syncope. This noninvasive procedure involves tilting a patient at 60 to 80 degrees for 10 to 60 minutes with or without an infusion of isoproterenol hydrochloride. A positive response reproduces the patient's symptoms in association with marked bradycardia, hypotension, or both. The mechanism for this faint involves the Bezold-Jarisch reflex. Some patients may respond to treatment directed at blocking certain aspects of this reflex arc (for example, β-blockers to blunt the endogenous catecholamine release).

The prevalence of psychiatric disorders in patients with syncope may be much higher (as high as 24%) than previously thought. Psychiatric syncope appears to consist predominantly of panic disorders and major depression. These patients tend to be younger; report more prodromal symptoms such as lightheadedness, shortness of breath, dizziness, and palpitations; and experience syncopal symptoms almost weekly. The mechanism of psychiatric syncope is probably multifactorial and ranges from hyperventilation to vasovagal syncope. Diagnosing and treating the psychiatric disorder may alleviate syncopal symptoms in some patients.

In the 1980s, a considerable percentage of patients were left with a diagnosis of "syncope of unknown origin." In the 1990s, physicians have an array of new diagnostic tests to select from and use to decipher the exact cause and treat patients who present with syncope.

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REFERENCES

Fujimura O, Yee R, Klein GJ, Sharma AD, Boahene KA: The diagnostic sensitivity of electrophysiologic testing in patients with syncope caused by transient bradycardia. N Engl J Med 1989; 321:1703-1707

Kapoor WN: Diagnostic evaluation of syncope. Am J Med 1991; 90:91-106

Kapoor WN: Evaluation and outcome of patients with syncope. Medicine 1990; 69:160-175

Linzer M, Felder A, Hackel A, et al: Psychiatric syncope: A new look at an old disease. Psychosomatics 1990; 31:181-188

Manolis AS, Linzer M, Salem D, Estes NA 3d: Syncope: Current diagnostic evaluation and management. Ann Intern Med 1990; 112:850-863

Primary Human Immunodeficiency Virus Infection—Will You Miss the Diagnosis?

THE PREVALENCE of human immunodeficiency virus (HIV) infection continues to increase. Worldwide, 9 to 11 million people are infected with HIV; by the year 2000, 40 million people may be infected. A new, unpublished study by the San Francisco Department of Health found a higher prevalence of HIV antibodies among gay men in the 17- to 25-year-old group compared with older gay men. According to the Centers for Disease Control, the number of cases of the acquired immunodeficiency syndrome (AIDS) associated with heterosexual transmission of HIV has been increasing steadily. The number of AIDS cases in drug injectors, women, and children is also on the rise. Most seroconverters—53% to 93% of homosexual men with new HIV infection—will have symptoms of primary HIV infection, and most (87%) will seek medical attention. These facts indicate that physicians will continue to see patients who have symptoms of acute HIV infection.

Recent studies have shown that primary infection with HIV is associated with high plasma levels of virus, enhancing potential infectivity. In 1992, people at risk for infection will come from two categories of transmission: sexually transmitted and blood-borne. New cases of acute HIV infection will occur in heterosexuals and homosexuals with multiple sexual contacts and in sexual partners of persons at risk, especially intravenous drug users. Blood-borne infection remains a risk for fetuses, neonates, drug injectors, and, less so, for transfusion recipients and health care workers with needle-stick injuries. The early recognition of primary HIV infection is important to allow counseling to prevent transmission and to begin early treatment and monitoring that can increase the length and quality of life.

Primary HIV infection causes a mononucleosis-like syndrome, with or without aseptic meningitis, associated with seroconversion for the HIV antibody. The incubation period before clinical illness has ranged from five days to three months. Clinical manifestations are of sudden onset, may last 3 to 14 days, and include fever, pharyngitis, lymphadenopathy, arthralgia, myalgia, headache, retro-orbital pain, nausea, vomiting, diarrhea, anorexia, oral thrush or ulcerations, and an erythematous maculopapular rash. Neurologic manifestations include meningoencephalitis, myelopathy, peripheral neuropathy, and the Guillain-Barré syndrome. The syndrome can mimic influenza, rubella, infectious mononucleosis, toxoplasmosis, viral hepatitis, syphilis, herpes simplex infection, or aseptic meningoencephalitis. Laboratory evaluation at this stage is frequently not diagnostic. Abnormal liver function test results, especially elevated alkaline phosphatase and aspartate aminotransferase levels, have frequently been reported. The lymphocyte count declines initially, followed by an inversion of the CD4/CD8 ratio and a progressive decline of CD4 cells.

The antibody test for HIV using enzyme immunoassay can be negative, making early diagnosis difficult. One recent example is a 39-year-old heterosexual man who had been attending "sex orgies" with multiple partners, and six weeks later severe headaches, neck stiffness, hypersomnolence, myalgias, generalized weakness, malaise, anorexia, and weight loss developed. After a two-week illness, he sought medical attention. Examination revealed diffuse adenopathy and nuchal rigidity; the results of routine laboratory tests